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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/714,692	11/16/2000	Kuo-Fen Lee	D6233CIP	5372

7590 12/16/2002

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/16/2002 13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/714,692	LEE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-27* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments and/or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 September 2002 (Paper No. 11) has been entered.

The amendment of 25 September 2002 (Paper No. 12) has been entered in full.

This application contains claims 1-19 and 24-27 drawn to an invention nonelected without traverse in Paper No. 4 (28 June 2001). A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20-23 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the specification at pg 2-3 of the previous Office Action (Paper No. 9, 20 March 2002) is *withdrawn* in view of the newly submitted Figure 1D (Paper No. 12, 25 September 2002).

2. The objection to the amendment that introduced new matter at pg 3 of the previous Office Action (Paper No. 9, 20 March 2002) is withdrawn in view of the amended description of Figures 4A-4D (Paper No. 12, 25 September 2002).

Claim Rejections - 35 USC § 112, first paragraph

3. Claims 20-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 20-23 are directed to a method of inhibiting angiogenesis in a target tissue comprising administering a Corticotropin Releasing Factor Receptor 2 (CRFR2) agonist to an individual having a pathophysiological condition selected from the group consisting of cancer and diabetic retinopathy. The claims also recite that the CRFR2 agonist is selected from the group consisting of urocortin and CRF and the target tissue is selected from the group consisting of heart, brain, pituitary, gonad, kidney, adipose, and gastrointestinal tract tissues. The basis for this rejection is set forth for claims 20-23 at pg 3-6 of the previous Office Action (Paper No. 9, 20 March 2002) and pg 3-5 of the Office Action of 13 August 2001 (Paper No. 5).

Applicant's arguments (Paper No. 12, 25 September 2002), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

Applicant asserts that in view of the data disclosed in the specification, one of ordinary skill in the art would conclude that well-known CRFR2 agonists such as urocortin and CRF could be used to inhibit angiogenesis. Applicant argues that the common methodologies of drug

treatment, such as IV infusion, that are well known in the art can be used in the instant invention. Applicant contends that for treatment of cardiovascular disease, one or ordinary skill in the art would readily employ methods of local transfer. Applicant submits that it is well known in the art that local transfer of agent by perivascular or intravascular delivery provides a way of enhancing arterioprotective endothelial functions without stimulating neovascularization at other sites.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, the specification of the instant application does not disclose the identity of any CRFR2 agonist capable of inhibiting angiogenesis in any target tissue in any subject with any pathophysiological condition. The specification outlines a prophetic procedure for inhibition of angiogenesis in a target tissue by administration of a CRFR2 agonist (pg 8, lines 6-10; pg 25, lines 19-21; pg 26, lines 1-4). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily inhibit angiogenesis in a target tissue. Although the specification discloses that agonists such as urocortin or CRF could be utilized in the claimed method, the skilled artisan must resort to trial and error experimentation to determine the optimal route of administration of the agonist, as well as the quality and duration of treatment in a subject. Such trial and error experimentation is considered undue.

Furthermore, relevant literature reports that many anti-angiogenic therapies, particularly for treating cancer, were highly active in animal models, but clinical results so far have been disappointing (Griffioen et al., Pharmacological Reviews 52(2): 237-268, 2000; pg 261, col.1, lines 1-2). In pathophysiological conditions, such as tumors, the percentage of proangiogenic

vessels is variable, often quite low, and hence anti-angiogenic therapy may only affect a minority of vessels (Griffioen et al., pg 262, pp 1). Additionally, strategies to target specific stages of disease progression require "an enormous preclinical research effort on the most potent formulations, dosing regimens, and so on" (pg 262, pp 1). Therefore, the skilled artisan would not necessarily be able to predict that administration of a CRFR2 agonist by any technique would inhibit angiogenesis in a tissue. Although Griffioen et al. do not specifically refer to the success or failure of general types of administration methodologies, Griffioen et al. emphasize that strategies to target stages of disease progression require preclinical research effort on formulations, dosing regimens, etc. Furthermore, the claims and the specification of the instant application do not recite a particular methodology of CRFR2 agonist administration. Undue experimentation would be required of the skilled artisan to determine the optimal route of agonist administration in an individual.

The state of the art is also such that the goal of delivering proteins and peptides noninvasively has only achieved modest success, with poor applicability to proteins and peptides (pg 343, col 1-2; Pettit et al. Trends Biotechnol 16: 343-349, 1998). The problems posed by proteins and peptides is their large molecular size, electrical charge, relatively hydrophilic nature, and relative instability in environments of extreme pH or proteolytic activity (such as the stomach and intestine) (pg 343, col 2). Pettit et al. review several routes of protein administration and the limitations that have been encountered. For example, proteins or peptides administered systemically must resist clearance via molecular filtration by the kidney and clearance by the reticuloendothelial system (pg 345, col 2). Simons et al. (Circulation 102(11) : e73-e86, 2000) also disclose that for treatment of cardiovascular disease, multiple delivery

modes remain unproven in terms of clinical efficacy and superiority (pg e80 (or 8), col 2). Simons et al. report that local perivascular delivery requires open-chest surgery, while intravenous infusions include systemic exposure to an agent (pg e79 (or 7), col 2). Therefore, the state of the prior art establishes the unpredictability of delivering proteins to a subject.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to inhibit angiogenesis by administration of a CRFR2 agonist and to determine the route, quantity, and duration of administration of the agonist, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the contradictory state of the prior art (see Griffioen et al., Pettit et al., and Simons et al.), and the unpredictability of the effects of a CRFR2 agonist on angiogenesis inhibition, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Bale et al. Proc Natl Acad Sci USA 99(11): 7734-7739, 2002.

Bale et al. J Neurosci 22(1) : 193-199, 2002.

This is a RCE of applicant's earlier Application No. 09/714,692. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB
Art Unit 1647
December 3, 2002

Elyabeth C. Kemmerer